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Synthesis and Structure of Spirocyclic Tetrahydrothiophene Derivatives Bearing a ‚Cage' Residue

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Trapping of the thiocarbonyl *S*-methanide **4** with tetracyanoethene and *N*-methylmaleimide led to the [3+2]-cycloadducts **11** and **12**, respectively. The structures of these cycloadducts were established by X-ray crystallography. The 1,3-dipole **4** has been generated by thermal decomposition of the corresponding 2,5-dihydro-1,3,4-thiadiazole **2**, which was prepared by the 1,3-dipolar cycloaddition of diazomethane with thioketone **1**.

Key words: thiocarbonyl ylides, 1,3-dipolar cycloaddition, tetrahydrothiophenes, 2,5-dihydro-1,3,4-thiadiazoles, polycyclic compounds, crystal structure

Thiocarbonyl *S*-methanides, generated conveniently by thermal elimination of nitrogen from 2,5-dihydro-1,3,4-thiadiazoles, are widely exploited in the synthesis of S-containing heterocycles via [3+2]-cycloadditions with suitable dipolarophiles [1,2]. They are classified as electron-rich 1,3-dipoles and, therefore, react smoothly with electron-poor dipolarophiles, such as acetylene dicarboxylates, fumarates, maleic anhydride, etc. However, thiocarbonyl compounds have been shown to exceed C,C-dipolarophiles in their reactivity toward thiocarbonyl ylides. For this reason, thioketones are called 'super-dipolarophiles' [3,4].

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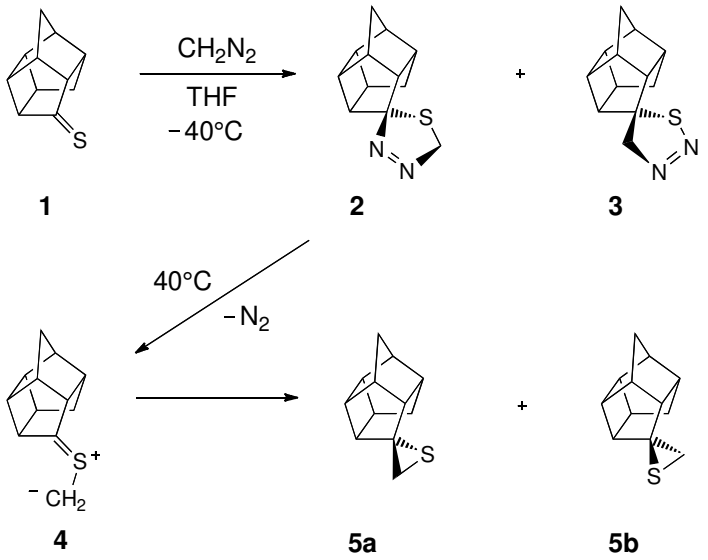
The mechanism of the formation of thiocarbonyl ylides from 2,5-dihydro-1,3,4-thiadiazoles was elucidated in the early 1980s' by Huisgen and coworkers, and in the following two decades, reactions with these dipoles have been eused xtensively for the synthesis of S-heterocycles (see [1,2]). The practical applications are limited by the availability of the corresponding thiadiazole derivatives, which are most conveniently accessible by the [3+2]-cycloaddition of diazo compounds with C=S groups. Most frequently, non-enolizable thioketones are used as the precursors, but the number of those compounds is rather small.

Recently, successful preparations of the new and stable polycyclic thioketone **1** were published [5,6]. It has been shown that **1** reacts easily with diazomethane at low temperature to yield the corresponding 2,5-dihydro-1,3,4-thiadiazole **2** as the major product along with the regioisomeric cycloadduct **3** [7] (Scheme 1). The isomers **2** and **3** could be separated neither by crystallization nor by preparative thin-layer chromatography (prep. TLC) on silica-gel. Upon heating the mixture in THF at 40°C **2** decomposed to thiiranes **5a** and **5b**, whereas the isomer **3** remained unchanged. This difference in the stability of **2** and **3** corresponds well with the results obtained with the analogous pair derived from adamantanethione [8]. We have shown that the intermediate thiocarbonyl *S*-methanide **4** can be trapped by C,C- and C,S-dipolarophiles [7].

Scheme 1

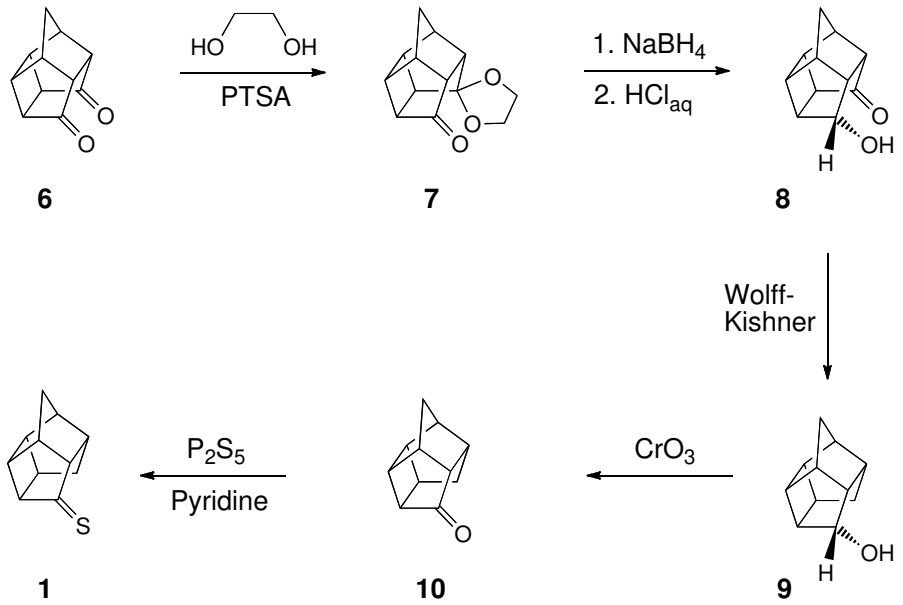


In the present paper, we report the structures of two cycloadducts obtained by the interception of **4** with tetracyanoethene and *N*-methylmaleimide, as well as a modified synthesis of the monoketone **10**, which is the starting material for the preparation of the thioketone **1**.

RESULTS AND DISCUSSION

The pentacyclic ketone **10** has been prepared by the four-step procedure shown in Scheme 2 (for other syntheses see [9-12]). Treatment of the commercially available diketone **6** with ethane-1,2-diol led to the monoacetal **7**, which was reduced with $NaBH_4$ to give, after hydrolysis, the hydroxy ketone **8**. Wolff-Kishner reduction and subsequent oxidation of the hydroxyl group gave **10** in an overall yield of 43.5%. Thionation of the latter by using P_2S_5 in pyridine gave the pentacyclic thioketone **1** [5].

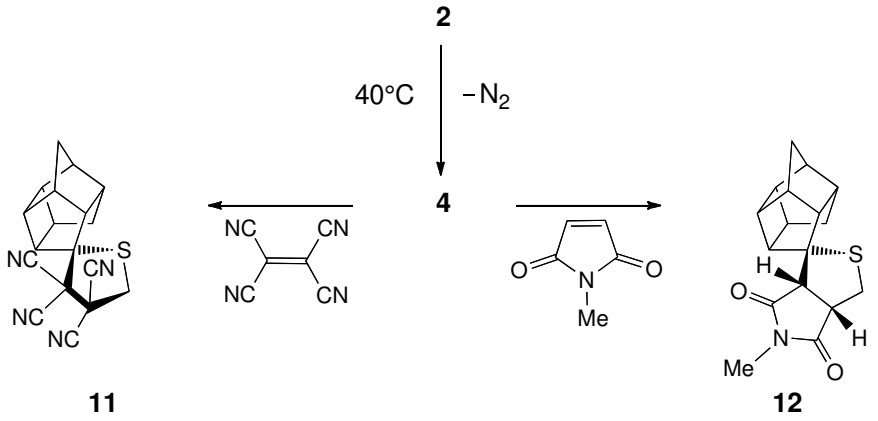
Scheme 2



Upon heating a mixture of **2** and **3** and tetracyanoethene or *N*-methylmaleimide in THF solution at 40°C nitrogen evolved, and subsequent separation of the reaction

mixture by prep. TLC yielded the [3+2]-cycloadducts **11** and **12**, respectively, as solid materials [7] (Scheme 3). From both reactions, only one stereoisomer of the cycloadduct was obtained. The spectroscopic data (MS, NMR, IR) and the elemental analyses were in accordance with the structures **11** and **12**. However, neither the configuration of the spiro-C-atoms nor the relative configuration of the fused heterocyclic system in **12** could be elucidated convincingly. Therefore, the structures were established by X-ray crystallography.

Scheme 3



Suitable crystals of **11** and **12** were grown from methanol and hexane/dichloromethane, respectively, by slow evaporation of the solvent at room temperature. The molecular structures of the two cycloadducts are shown in Figures 1 and 2. In both compounds, the S-atom of the thiophene ring is *endo*-oriented with respect to the 'cage' residue. This feature indicates that the dipolarophiles approached the thiocarbonyl *S*-methanide **4** from the *exo*-side selectively. Most likely, the same orientation can be attributed to all [3+2]-cycloadducts obtained with **4** [7]. Similarly, it can be proposed that 1,3-dipoles approach the C=S group of the parent thioketone **1** also from the *exo*-side, as suggested for products **2** and **3** (Scheme 1).

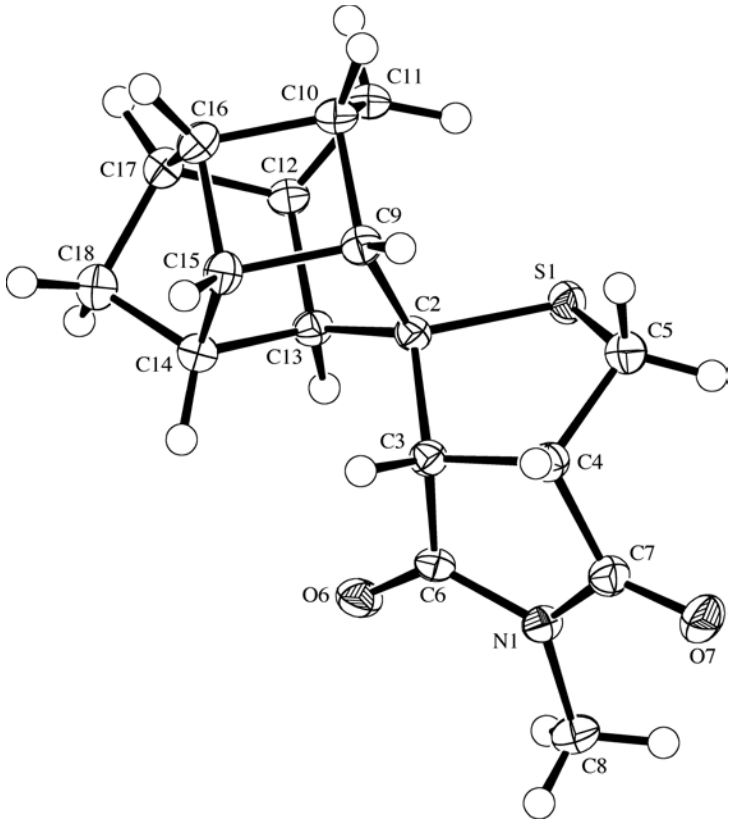


Figure 1. ORTEP-Plot [13] of the molecular structure of **11** (arbitrary numbering of the atoms; 50% probability ellipsoids)

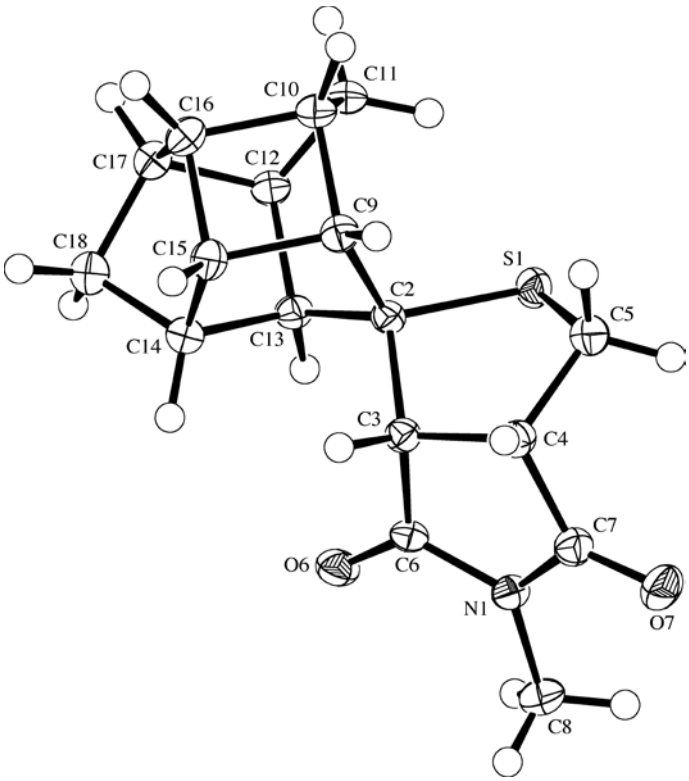


Figure 2. ORTEP-Plot [13] of the molecular structure of **12** (arbitrary numbering of the atoms; 50% probability ellipsoids)

In each structure, the tetrahydrothiophene ring has a half-chair conformation twisted on C(2)-C(3) in the case of **11** and on S(1)-C(2) in **12**. The two heterocyclic five-membered rings in **12** are *cis*-fused, and the pyrrolidine ring occupies the *endo* position with respect to the 'cage' residue.

In conclusion, the easily accessible thiocarbonyl *S*-methanide **4** bearing a 'cage' residue undergoes smooth [3+2]-cycloadditions with electron deficient C=C dipolarophiles, which add from the *exo*-side of the reactive intermediate.

EXPERIMENTAL

1. General. See [7].

2. Starting materials. Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**6**) is commercially available from Sigma-Aldrich or can be prepared following a protocol in [14]. Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one (**10**) [11] was obtained from **6** according to a modified 4-step protocol outlined below. Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-thione (**1**) was synthesized by thionation of **10** using phosphorus pentasulfide as a thionating reagent and pyridine as a solvent [5] (see also [6], where the application of Lawesson's reagent is described).

3. Synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one (10). A mixture of **6** (20 g, 0.115 mol), ethene-1,2-diol (9 g), *p*-toluenesulfonic acid (0.25 g), and benzene (80 ml) was refluxed (Dean Stark trap) for 5 h. Then, the mixture was cooled and slowly poured into an ice cold aqueous sodium carbonate solution (50 ml, 10%). Extraction with CH_2Cl_2 gave crude monoketal **7** as a colorless solid (21 g, 83.8%).

To an ice cold solution of **7** (21 g, 0.096 mol) in ethanol (120 ml), a cold solution of sodium borohydride (7 g in 50 ml of EtOH) was added under stirring within 5 min. The mixture was left for 2 h in the ice bath and kept for another 2 h at room temperature. Then, the mixture was again cooled in an ice bath, HCl (300 ml, 10%) was added cautiously, and the solution was stirred for an additional 2 h at room temperature. Extraction with CH_2Cl_2 yielded hydroxyketone **8** [12,15] (15 g, 88.5%).

The hydroxyketone **8** (15 g, 0.085 mol) and hydrazine hydrate (22 ml, 98%) in diethyleneglycol (200 ml) was heated at 120°C for 1.5 h. The mixture was allowed to cool for 5 min, potassium hydroxide (11 g) was added, and the mixture was slowly heated to 190°C (internal temperature). The excess hydrazine hydrate and water was distilled off ovewr ca. 3 h (until the distillation is complete). Extraction with Et_2O gave alcohol **9** [9] (11 g, 80.0%).

To a stirred solution of chromium trioxide (13 g) in water (12 ml) and acetic acid (150 ml, 98%), a solution of **9** (11 g, 0.068 mol) in acetic acid (50 ml) was added dropwise within 10 min. The solution was heated at 90°C for 4 h, cooled to room temperature and diluted with water (600 ml). The mixture was extracted with CH_2Cl_2 and the extract was washed first with saturated aqueous sodium hydrogen carbonate and then with water. Dichloromethane was removed and the crude product was purified by filtration through silica gel (100-150g) using a mixture of hexane and CH_2Cl_2 (4:1) as eluent. Monoketone **10** (8.0 g, 73.5%) was obtained as a colorless solid with m.p. 193-196°C ([16]: m.p. 194-196°C). Overall yield from **6**: 43.5%.

4. Preparation of cycloadducts 11 and 12. A crude mixture of 2,5-dihydro-1,3,4-thiadiazolidines **2** and **3**, which had been obtained from **1** and a solution of diazomethane in Et_2O, was used for the reactions with tetracyanoethylene and *N*-phenylmaleimide according to [7]. Crystals of *3',3',4',4'-tetracyanospiro[pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,2'-tetrahydrothiophene]* (**11**) and *7-methylspiro[7-aza-2-thiabicyclo[3.3.0]-octane-2,8'-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-6,8-dione* (**12**) suitable for the crystal-structure determination were grown by slow evaporation of the solvents of solutions in methanol or hexane/CH_2Cl_2, respectively, at room temperature.

5. X-Ray Crystal-Structure Determination of 11 and 12 (see Table 1 and Figs. 1 and 2)*). All measurements were made on a Nonius KappaCCD diffractometer [17] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reduction was performed with HKL Denzo and Scalepack [18]. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method [19] was applied. Equivalent reflections were merged. Data collection and refinement parameters are given in Table 1, and views of the molecules are shown in Figs. 1 and 2. The structures were solved by direct methods using SIR92 [20], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the Me group of **12**). Refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2-F_c^2)^2$. A correction for secondary extinction was applied for **11**. In the case of **12**, two reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from [21a], and the scattering factors for H-atoms were taken from [22]. Anomalous dispersion effects were included in F_c [23]; the values for f' and f'' were those of [21b]. The values of the mass attenuation coefficients are those of [21c]. All calculations were performed using the SHELXL97 [24] program.

Acknowledgement

*) CCDC-258336-258337 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* **www.ccdc.cam.ac.uk/conts/retrieving.html** (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Table 1. Crystallographic Data for Compounds **11** and **12**

	11	**12**
Crystallized from	MeOH	hexane/CH_2Cl_2
Empirical formula	$C_{18}H_{14}N_4S$	$C_{17}H_{19}NO_2S$
Formula weight [g mol^{-1}]	318.40	301.40
Crystal color, habit	colorless, prism	colorless, prism
Crystal dimensions [mm]	0.12 × 0.32 × 0.35	0.10 × 0.15 × 0.30
Temperature [K]	200(1)	160(1)
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
Z	4	4
Reflections for cell determination	22486	20675
2θ range for cell determination [°]	4–60	4–55
Unit cell parameters a [Å]	13.6143(2)	8.3619(2)
b [Å]	8.9468(1)	6.3673(1)
c [Å]	13.2517(2)	25.6655(6)
β [°]	113.8855(7)	92.024(1)
V [Å^3]	1475.88(4)	1365.65(5)
D_X [g cm^{-3}]	1.433	1.466
μ(Mo$K\alpha$) [mm^{-1}]	0.224	0.241
Scan type	ϕ and ω	ϕ and ω
$2\theta_{(max)}$ [°]	60	55
Transmission factors (min; max)	0.841; 0.975	0.868; 0.977
Total reflections measured	41269	27072
Symmetry independent reflections	4320	3130
Reflections with $I > 2\sigma(I)$	3253	2392
Reflections used in refinement	4320	3128
Parameters refined	209	191
Final $R(F)$ [$I>2\sigma(I)$ reflections]	0.0418	0.0416
$wR(F^2)$ (all data)	0.1102	0.1086
Weights:[a)] a; b	0.0506; 0.5074	0.0466; 0.9298
Goodness of fit	1.044	1.049
Secondary extinction coefficient	0.008(2)	-
Final Δ_{max}/σ	0.001	0.001

$\Delta\rho$ (max; min) [e Å^{-3}]	0.37; -0.29	0.32; -0.30

[a)] $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$